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The early onset of sero-negative polyarthritis juvenile idiopathic arthritis in female patient — a case report

**Short title:** The early onset of sero-negative polyarthritis JIA in female patient

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#### **Abstract**

**Background:** Juvenile idiopathic arthritis (JIA) is a chronic inflammatory joint disease with a complex etiology. It is characterised by symptoms such as swelling, exudates, soreness, and reduced mobility. Early diagnosis and treatment are crucial to improving long-term prognosis and preventing complications.

**Case presentation:** A 5-year-old girl with polyarticular seronegative, human leukocyte antigen B27 (HLA-B27)-positive JIA previously under the care of another medical centre was admitted for evaluation of disease activity and possible reintroduction of treatment. The patient's history began at the age of 14 months when symptoms of inflammation of the small joints of the hands appeared.

On physical examination pain and swelling of the proximal interphalangeal joints of the hands were detected. Laboratory tests revealed low inflammatory indices. Rheumatoid factor, anticitrullinated protein antibodies, and a genetic test for HLA-Cw6 were negative. An ultrasound of the hands confirmed the presence of arthritis. Furthermore, a magnetic resonance imaging (MRI) scan and a computed tomography (CT) scan were performed, revealing sacroiliitis. The treatment initially included two disease-modifying drugs — methotrexate and sulphasalazine with folic acid shielding. Subsequently, due to the poor response to treatment, the child was

qualified for biological treatment with adalimumab, achieving a significant improvement in clinical condition and imaging findings. Follow-up hospital admissions confirmed the stabilisation of the patient's condition and the absence of disease progression.

**Conclusion:** This case emphasises the importance of early diagnosis and an individualised therapeutic approach in the treatment of JIA. Biological therapy with adalimumab, combined with conventional drugs, proved effective in controlling the disease's symptoms and improving the patient's quality of life.

Key words: juvenile idiopathic arthritis; MRI; adalimumab; musculoskeletal system

### Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in the pediatric population [1], with an estimated prevalence of about 1 per 1,000 children and an incidence that ranges from 2 to 28 per 100,000 pediatric population — nearly 10 per 100,000 pediatric population in Poland [2]. It is a heterogeneous group of idiopathic inflammatory arthritis, differing in etiopathogenesis and clinical presentation. There is a significant disparity between the genders within JIA patients, with women developing the disease more often than men (female-to-male ratio of 1:0.57) [3].

The common feature and basic diagnostic according to The International League of Associations for Rheumatology (ILAR) criterion [4] of JIA is arthritis of an unexplained etiology that occurred before the age of 16, with symptoms such as swelling, exudates, soreness, and reduced mobility present for a minimum of six weeks. The diagnosis is to be made only after excluding other causes of arthritis from the so-called "exclusion list" consisting of infectious, reactive, allergic, and toxic arthritis, proliferative diseases, other inflammatory connective tissue diseases, arthropathies of blood and metabolic diseases, systemic non-inflammatory connective tissue diseases, arthropathies of immune diseases, psychogenic gout and fibromyalgia [5]. There are seven JIA subtypes: oligoarthritis, seropositive polyarthritis, seronegative polyarthritis, systemic arthritis, enthesitis-related arthritis, juvenile psoriatic arthritis, and undifferentiated [4]. The laboratory blood tests are not intended to provide a diagnosis of JIA but to exclude potential other medical conditions. These may also be valuable for determining the type of JIA and monitoring its course. The most commonly determined parameters are inflammatory markers such as white blood cell count (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). The

immunological tests commonly performed include antinuclear antibodies (ANA), rheumatoid factor (RF), and antibodies to cyclic citrullinated peptide (anti-CCP) [6]. The determination of RF separately 2 times at least 3 months apart indicates whether a person is seropositive or seronegative. Around 85% of polyarthritis patients are RF-negative [7]. Imaging techniques such as ultrasound (USG), X-ray, computed tomography (CT), and magnetic resonance imaging (MRI) are applicable in the diagnosis and monitoring of JIA [8-9].

Treatment of JIA is complex and requires a comprehensive, multifaceted approach to effectively control symptoms, prevent joint damage, and improve patients' quality of life. Current pharmacotherapy should be guided by the 2019 ACR recommendations [10]. According to these recommendations, patients with active polyarticular JIA should be treated with disease-modifying antirheumatic drugs (DMARDs) from the beginning instead of non-steroidal anti-inflammatory drugs (NSAIDs) as in the past. The preferred drug is methotrexate (MTX). Systemically administered glucocorticosteroids (GCs) can only be used as bridging therapy for no longer than 3 months until the full effect of MTX becomes apparent in patients with high disease activity. Subsequently, in the case of low disease activity, treatment can be escalated by delivering injections of GCs, increasing the dose of the DMARD, or switching it to MTX if it has not been administered before. In the case of high or moderate JIA activity, a biologic drug should be included.

Despite treatment development observed in recent years, JIA still reduces the quality of life of patients, and only around 20–25% of them will experience complete remission. The prognosis depends on the activity of the disease and also differs for the different subtypes. In about half of the patients, the disease remains active into early adulthood, and as many as 30% face disability [11].

### Case presentation

In September 2021, a European white girl aged 5 years and 2 months with a diagnosis of polyarticular juvenile idiopathic arthritis (seronegative form), human leukocyte antigen B27 (HLA-B27)-positive, was admitted to the Clinical Department of Pediatrics and Rheumatology at the St. Louis Regional Specialized Children's Hospital in Krakow for disease monitoring and possible initiation of treatment. The child had previously been treated in another clinical center. At the time of admission, the patient did not receive any medications — the mother reported that she had independently withdrawn MTX due to the child's abdominal complaints of nausea and vomiting.

In medical history, the first symptoms of the disease were observed at the age of 14 months consisting of widening of the outline of the interphalangeal joints of fingers II-IV of the right hand and I–IV of the left hand, normal mobility. A USG of the right hand performed during the patient's hospitalisation in November 2017 showed metacarpophalangeal (MCP) joints III and IV, proximal interphalangeal (PIP) joints II and III, and flexor tendon sheaths of fingers III and IV. In the left hand, effusion in the interphalangeal (IP) joint of the thumb, MCP joint II, and distal interphalangeal (DIP) joint IV was visible. Due to the confirmation of arthritis of the small joints of the hands with involvement of the tendon sheaths, the first-line treatment of JIA [12] —NSAIDs and prednisone at a dose of 5 mg — was applied, concomitantly, MTX was included at a dose of 2.5 mg twice a week with folic acid protection. During follow-up at the Rheumatology Clinic in May 2018, prednisone was discontinued, and chloroquine was included due to the lack of clinical improvement.

In order to assess the effectiveness of treatment and to determine further management, the child was consecutively hospitalised in July 2018. Physical examination on admission revealed swelling and limitation of mobility of the right wrist, slight swelling of the left wrist, swelling and flexion contracture of the PIP II–IV joints of the right hand, swelling and flexion contracture of the PIP I and III and DIP III joints of the left hand. On the USG of the right hand, there was an exudate in the PIP II-IV joint cavities and a moderately thickened synovial membrane without features of excessive vascularisation. The thickened synovial membrane of the flexor tendon sheath of finger IV was noticeable. The USG of the left hand showed exudate, moderately thickened synovial membrane in the IP joint cavity of the thumb, without features of increased vascularisation, as well as thickened synovial membrane of the flexor tendon sheaths of fingers I and III. X-ray of the hands was also performed, which showed the presence of a geode in the hook bone of the right wrist and marked periosteal build-up in the proximal phalanx of the proximal phalanges of the third and fourth fingers of the right hand and the third finger of the left hand. In laboratory tests performed, inflammatory parameters were low [WBC — 8.99 thousand/ $\mu$ L (4.86–18.18), ESR 4 mm/h (< 12), CRP 5 mg/L [1-10]), blood count, liver and renal parameters were in normal range. The presence of HLA-B27 antigen and anti-nuclear antibodies with homogeneous luminescent type in low titer (1:160) was detected, and RF was absent. Concomitant hepatitis C virus (HCV) infection was excluded. In the absence of the expected improvement, treatment was intensified — the dose of MTX was increased to 10 mg once a week, systemic steroids were reintegrated prednisone at a dose of 5mg for 2 weeks with a planned dose reduction. In August 2018, due

to the ineffectiveness of the previous treatment, the patient was qualified for biologic treatment with tocilizumab at a dose adjusted to the child's weight.

Given the lack of clinical improvement after 6 months of tocilizumab therapy and the persistence of high disease activity, the biologic drug was changed to adalimumab at a dose of 20 mg. Treatment was continued until February 2021, with initially observed improvement.

On physical examination on admission to the Clinical Department of Pediatrics and Rheumatology at the St. Louis Regional Specialized Children's Hospital in Krakow in September 2021, pain and swelling of the PIP II and III joint of the right hand and the PIP of the left hand were found, other joint contours were not enlarged, active and passive mobility was preserved, strength and muscle tone were normal. A family history consisted of psoriasis in the mother, mother's sister, and mother's father. No significant abnormalities were found in laboratory tests performed during the hospitalisation, low inflammatory indices [WBC — 10.34 thousand/μL (4.86–13.18), CRP < 5 mg/L [0–10], ESR — 8 mm/h (< 12), RF, anti-CCP and genetic test for HLA-Cw6 were negative. Insufficient vitamin D level (23.2 ng/mL). Densitometry results were within reference values for the patient's sex and age. An electrocardiogram (ECG) recording, chest X-ray, and abdominal USG proved to be normal. The patient was consulted ophthalmologically - uveitis was excluded. USG of hip, knee, and foot joints did not reveal pathology. The USG of the hand joints on the left side revealed trace effusion in DIP I, synovial membrane, and flow normal, as well as MCP II, synovial membrane, and grade I trough. A performed whole-body MRI detected an irregular zone of bone marrow edema located in the sacrum on the left side, adjacent to the sacroiliac joint crevice — the image suggested the presence of an active inflammatory process. In addition, an enhancing foci of inflammatory granuloma character is symmetrically distinguished on the right side. The imaging diagnosis was extended by performing a CT scan of the sacroiliac joints with contrast (Fig. 1).

Due to the active inflammatory process in the sacroiliac and hand joints, it was decided to restart two DMARDs — MTX at a dose of 15 mg per week and sulphasalazine at a dose of 500 mg per day with folic acid shielding, with good tolerance. Re-hospitalisation has been scheduled for October 2021.

On admission, the child was then presented with pain and swelling of the PIP II and III joints of the right hand and the PIP of the left hand. In September 2021, due to an exacerbation of the disease process, the girl was qualified on an outpatient basis for resumption of biological

treatment. In laboratory tests, there were no abnormalities. During hospitalisation, the first dose of the biological drug, adalimumab, was administered without complications. The treatment of MTX at a dose of 15 mg per week and sulfasalazine at a dose of 500mg per day with folic acid shielding was maintained.

The patient was hospitalised again in March 2022 to assess the effectiveness of the biological treatment. The mother reported pain in the toes during gait and at rest, gait disturbance, especially in the morning, and the child's limp since 01.2022. On physical examination, the contours of the left thumb and fingers II-IV of both hands were widened, painless, active, and passive mobility was preserved, and the contours of the other joints were not widened. Painfulness of fingers and V toe of both lower limbs was reported, and strength and muscle tone were normal. Walking abnormalities were present — wide-base walking and limping. In laboratory tests performed during hospitalisation, inflammatory indices were low [CRP — 5 mg/l (0–10), ESR — 7 mm/h, WBC — 7.13 thousand/uL (4.86–13.18)], low vitamin D3 level (26.4 ng/dL), liver and renal parameters normal. The USG of the hip and knee joints showed no abnormalities. USG of the joints of the hands presented a small effusion with low inflammatory activity (first stage flow) in the DIP I of the left hand and a persistent thickening of the sheath of finger III on the left side without effusion (first stage flow). Given the results obtained and the child's clinical condition, the disease activity was assessed as low, and the effectiveness of the treatment administered was confirmed. Continuation of current pharmacotherapy and rehabilitation was recommended. Due to hyperactivity, the patient has been under the care of a psychiatric outpatient clinic since June 2023, where fluoxetine has been included in the treatment.

In February 2024, the child was administered to our department for follow-up examinations and a planned MRI of the sacroiliac joints. The girl is taking MTX 15 mg once a week in folic acid shielding, fluoxetine 10 mg daily, and vitamin D 3000 IU per day. She was also treated with adalimumab 40mg every 2 weeks. Outpatient sulfasalazine was withdrawn in 2023. On physical exam, on admission, the contours of the left thumb and fingers III-IV were widened, in the right II, III, and IV fingers were widened, no pain, active and passive mobility was preserved, otherwise joint contours were not widened, full prone, incomplete squat, strength, and muscle tone were normal, walking on a wide base. In laboratory tests, low inflammatory markers [CRP — 2.5 mg/L (0–5), WBC — 7.26 thousand/uL (4270–1140)] and insufficient vitamin D3 levels (27.8 ng/mL). A follow-up MRI of the sacroiliac joints showed no areas of significant marrow edema, sclerosis, or fatty remodeling in the subchondral layers of the

joints (Fig. 2). The clinical picture and findings indicate a stationary disease state, and therefore, treatment was not modified.

#### **Discussion**

The patient presented in this case report meets the criteria for RF-negative polyarticular JIA according to the ILAR classification. This is evidenced by an onset of disease involving seven joints of the hands lasting more than 6 months, with persistent RF negativity. Gender, age of onset, and symmetrical involvement of the small joints of the hands are also characteristic of this disease subtype [13]. The clinical picture showed no general symptoms such as fever, hepato- and/or splenomegaly, lymphadenopathy, or respiratory, gastrointestinal, or circulatory system involvement.

Clinically, the child presented with typical symptoms of arthritis, such as swelling, pain, restricted mobility, and a tendency to flexion contracture. A range of laboratory tests and imaging techniques were used in the diagnostic process. Regular assessments of inflammatory parameters such as ESR, CRP, and WBC were performed, and they remained low throughout the disease course, which is characteristic of seronegative polyarticular JIA. Immunological tests such as RF, ANA, and anti-CCP were also conducted with negative results. Determination of these antibodies can be crucial in the diagnostic process, in the classification of the JIA subtype, and in the assessment of the patient's prognosis [11].

General urinalysis and liver and renal function assessment were also performed periodically for possible detection of amyloidosis secondary to JIA [14]. In the present child, these parameters tended to be within the normal range. Genetic tests for HLA-B27 (positive) and HLA-Cw6 (negative) were also performed due to a family history of psoriasis [15]. In terms of diagnostic imaging, a regular USG assessment of the joints was provided. USG makes it possible to visualize the thickening of the synovial membrane and tendon sheaths, increased blood flow due to hypervascularisation, as well as exudate in the joint cavity, tendon sheath, and synovial bursae. This allows non-invasive, rapid, and low-cost verification of the presence of joint inflammation without requiring general anaesthesia, which is particularly important in younger children. This makes USG a valuable tool not only to aid diagnosis but also to assess the risk of disease relapse and to monitor the effectiveness of treatment [16]. As the aforementioned changes suggestive of inflammation in the joints of the patient's hand persisted, the decision was made to extend the diagnostics with whole-body MRI to assess the

activity of the disease and to detect possible inflammatory lesions in other joints, with particular emphasis on joints that could not be evaluated by USG. Due to the presence of marrow edema in the sacroiliac joints, the assessment was expanded with a scan aimed at exclusively imaging these joints. CT and MRI are crucial in diagnosing and monitoring sacroiliitis in children. CT is useful for detecting structural changes such as erosions and bone remodelling [17]. MRI is the preferred modality considering its lack of radiation, high sensitivity in detecting early inflammatory changes, and ability to accurately assess soft tissues such as synovial membrane and ligaments. However, taking into account the better availability of CT than MRI at the clinic where the child was hospitalized, the decision to perform a contrast-enhanced CT scan was made, confirming the sacroiliitis. During the course of treatment, MRI scans of the sacroiliac joints were performed to monitor its efficacy and, thus, disease activity in this area, where features of acute inflammation were no longer observed. MRI offers high-resolution imaging of soft tissues, enabling the detection of early inflammatory changes and their accurate assessment, as well as the evaluation of disease activity without exposure to ionising radiation [17]. With these features, MRI allows precise and safe tracking of therapy effects [18].

The treatment in the presented case was initiated with MTX at the dose of 2.5 mg twice a week, NSAIDs, and bridging therapy with systemic GCs due to the high disease activity. Subsequently, a second DMARD, chloroquine, was added due to a lack of improvement. After nine months, due to the persistent poor response, the therapy was escalated by increasing the dose of MTX to 10 mg once a week, chloroquine was discontinued, prednisone was restarted as bridging therapy. The patient was qualified for biologic therapy with the interleukin 6 (IL-6) antagonist — tocilizumab; next, due to the lack of efficacy, the drug was changed to tumor necrosis factor inhibitor (TNFi), but after two years, the therapy was discontinued for 6 months. The resumption of treatment began with the reintroduction of two DMARDs - MTX and sulfasalazine, after which the child was again qualified for the inclusion of biological treatment - adalimumab. Treatment was managed with significant improvement observed, and the disease transitioned to a stationary state.

Attention should also be drawn to the necessity of multi-specialist care in children with JIA. In addition to pediatricians' and rheumatologists' care, ophthalmological care is equally important. Within the group of children with JIA, uveitis is the most common extra-articular manifestation of the disease. The incidence reaches 5-10% of those with polyarthritis [19].

## **Conclusion:**

Early diagnosis and appropriate treatment of JIA are essential to improving a patient's prognosis. An individualised therapeutic approach, supported by a multidisciplinary team, ensures optimal disease management. Advanced diagnostic modalities, such as MRI, CT, and USG, allow a precise assessment of the inflammation, enabling proper diagnosis and optimal treatment monitoring.

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Figures:

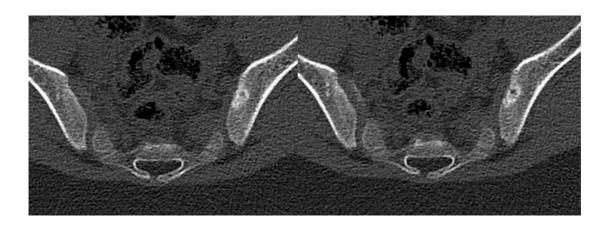


Figure 1

Computed tomography (CT) of the sacroiliac joints showing symmetrical bilateral lesions of acute inflammation (sacroiliitis) and chronic lesions in the form of erosions in the anteroinferior parts of the joints.

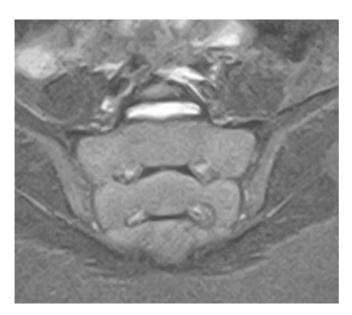


Figure 2

MRI of the sacroiliac joints in STIR-sequence showing no signs of sacroiliitis.